

FORM PTO-1199 (Modified)
(REV 11-98)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES

FLA-0048

DESIGNATED/ELECTED OFFICE (DO/EO/US)

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

CONCERNING A FILING UNDER 35 U.S.C. 371

09/647290

INTERNATIONAL APPLICATION NO.

INTERNATIONAL FILING DATE

PRIORITY DATE CLAIMED

PCT/EP99/01795

18 March 1999

30 March 1998

TITLE OF INVENTION

TRANSDERMAL THERAPEUTIC SYSTEM WHICH CONTAINS A D2 AGONIST AND WHICH IS PROVIDE D FOR TREATING PARKINSONISM, AND A METHOD FOR THE PRODUCTION THEREOF

APPLICANT(S) FOR DO/EO/US

MÜLLER, Walter et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Return Post Card

"Express Mail" Label No. EL550128374US
Date of Deposit 28 September 2000

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Box PCT, Washington, D.C. 20231.

By Deborah Ehret
Typed Name: Deborah Ehret

097647290

PCT/EP99/01795

FLA-0048

21. The following fees are submitted.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$970.00
- ☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$840.00
- ☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$690.00
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$670.00
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) \$96.00

ENTER APPROPRIATE BASIC FEE AMOUNT =

\$840.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).

\$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	24 - 20 =	4	x \$18.00	\$72.00
Independent claims	2 - 3 =	0	x \$78.00	\$0.00
Multiple Dependent Claims (check if applicable).				<input type="checkbox"/> \$0.00

TOTAL OF ABOVE CALCULATIONS =

\$912.00

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (check if applicable).

☐

\$0.00

SUBTOTAL =

\$912.00

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).

\$0.00

TOTAL NATIONAL FEE =

\$912.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).

☐

\$0.00

TOTAL FEES ENCLOSED =

\$912.00

Amount to be:
refunded
charged

\$

\$

- ☐ A check in the amount of _____ to cover the above fees is enclosed.
- ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.
A duplicate copy of this sheet is enclosed.
- ☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **12-1086** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Jane Massey Licata, Reg. No. 32,257
Law Offices of Jane Massey Licata
66 E. Main Street
Marlton, New Jersey 08053
Telephone: (856) 810-1515
Facsimile : (856) 810-1454

SIGNATURE

LICATA, Jane Massey

NAME

32,257

REGISTRATION NUMBER

28 September 2000

DATE

09/647290
526 Rec'd PCT 28 SEP 2000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: FLA-0048

Inventors: Mueller and Peck

International
Application No.: PCT/EP99/01795
U.S. Serial No.: N/A

International
Filing Date: 30th March 1998
U.S. Filing Date: Herewith

Title: Transdermal Therapeutic System Which
Contains a D2 Agonist and Which is
Provided for Treating Parkinsonism and a
Method of Production Thereof.

"Express Mail" Label No. EL550128374US
Date of Deposit 28 September 2000

I hereby certify that this paper is being deposited
with the United States Postal Service "Express Mail
Post Office to Addressee" service under 37 CFR 1.10
on the date indicated above and is addressed to the
Assistant Commissioner for Patents, Box PCT,
Washington, D.C. 20231.

By

Deborah Ehret
Typed Name: Deborah Ehret

Assistant Commissioner for
Patents
Box PCT
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-referenced application as follows:

IN THE CLAIMS:

Cancel claims 1-17 and replace them with the following new claims:

-- 18. A transdermal therapeutic system comprising a self-adhesive matrix layer containing (-)-5,6,7,8-tetrahydro-6-[propyl-1[2-(2-thienyl) ethyl]amino]-1-naphthalenol in an effective amount wherein the matrix is based on a non-aqueous, acrylate-based or silicone-based polymer adhesive system having a solubility of $\geq 5\%$ (w/w) for (-)-5,6,7,8-tetrahydro-6-[propyl-1[2-(2-thienyl) ethyl]-amino]-1-naphthalenol, and wherein said matrix is substantially free of inorganic silicate particulates; a backing layer inert to the components of the matrix layer; and a protective foil or sheet covering the matrix layer to be removed prior to use.

19. The transdermal therapeutic system of claim 18 further comprising $< 0.5\%$ (w/w) inorganic silicate particulates in the matrix layer.

20. The transdermal therapeutic system of claim 18 further comprising $< 0.05\%$ (w/w) inorganic silicate particulates in the matrix layer.

21. The transdermal therapeutic system of claim 18 wherein the acrylate-based polymer adhesive in the matrix layer contains at least two monomers selected from the group of acrylic acid, acrylamide, hexylacrylate, 2-ethylhexylacrylate, hydroxyethylacrylate, octylacrylate, butylacrylate, methylacrylate, glycidylacrylate, methacrylic acid, methacrylamide, hexylmethacrylate, 2-ethylhexylmethacrylate, octylmethacrylate, methylmethacrylate, glycidylmethacrylate, vinylacetate and vinylpyrrolidone.

22. The transdermal therapeutic system of claim 18 wherein the silicone-based polymer adhesive in the matrix layer further comprises additives to enhance the solubility of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl) ethyl]amino]-1-naphthalenol in the form of hydrophilic polymers or glycerol or glycerol derivatives.

23. The transdermal therapeutic system of claim 21 wherein the acrylate-based polymer contains between 10 to 40% (w/w) (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl) ethyl]-amino]-1-naphthalenol.

24. The transdermal therapeutic system of claim 22 wherein the silicone-based polymer adhesive contains between 5 to 25%

(w/w) (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl) ethyl]-amino]-1-naphthalenol.

25. The transdermal therapeutic system of claim 23 further comprising substances which enhance the permeation of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl) ethyl]amino]-1-naphthalenol into the human skin.

26. The transdermal therapeutic system of claim 24 further comprising substances which enhance the permeation of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl) ethyl]amino]-1-naphthalenol into the human skin.

27. The transdermal therapeutic system of claim 25 wherein the permeation-enhancing substance is selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerol or its derivatives, N-methyl-pyrrolidone, terpenes, and terpene derivatives.

28. The transdermal therapeutic system of claim 26 wherein the permeation-enhancing substance is selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerol or its derivatives, N-methyl-pyrrolidone, terpenes, and terpene derivatives.

29. The transdermal therapeutic system of claim 27 wherein the permeation-enhancing substance is oleic acid or oleyl alcohol.

30. The transdermal therapeutic system of claim 28 wherein the permeation-enhancing substance is oleic acid or oleyl alcohol.

31. The transdermal therapeutic system of claim 22, wherein the hydrophilic polymer is selected from the group of polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinylacetate, polyethyleneglycol, polypropylene glycol, and a copolymer of ethylene and vinylacetate.

32. The transdermal therapeutic system of claim 31 wherein the hydrophilic polymer is soluble polyvinylpyrrolidone, and wherein the soluble polyvinylpyrrolidone is present in the active substance-containing matrix layer at a concentration of between 1.5 and 5% (w/w).

33. The transdermal system of claim 18 wherein the matrix further comprises inert fillers to improve cohesion.

34. A process for preparing a transdermal therapeutic system, comprising the steps of:

i. mixing a suspension of (-)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl) ethyl]amino]-1-naphthalenol hydrochloride in ethanol with an alkaline compound in ethanol to convert the hydrochloride into the free base;

ii. adding polyvinylpyrrolidone and a solution of an adhesive and

iii. drying the product.

35. The process of claim 34 further comprising the step of filtering the resultant suspension in step i.

36. The process of claim 34 wherein the alkaline compound is sodium hydroxide or potassium hydroxide.

37. The process of claim 34 wherein the alkaline compound is sodium metasilicate or potassium metasilicate.

38. The process of claim 34 wherein the alkaline compound is sodium trisilicate or potassium trisilicate.

39. The process of claim 34 wherein the mixture is spread on an inert backing layer or protective foil or sheet in such a manner as to produce a uniform film prior to drying the product.

40. A product made in accordance with the process of claim 34.

Preliminary Amendment
PCT/EP99/01795
Attorney Docket No: FLA-0048
Page 7

41. A product made in accordance with the process of claim
35. --

Remarks

Pending claims 1-17 in the PCT/EP99/01795 have been canceled and replaced with new claims 18-41 to conform the claims to U.S. practice for entry into national phase. No new matter has been added.

Respectfully submitted,

Jane Massey Licata

Jane Massey Licata
Registration No. 32,257

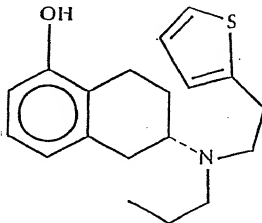
Date: September 28, 2000

Law Offices of
JANE MASSEY LICATA
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

TRANSDERMAL THERAPEUTIC SYSTEM WHICH CONTAINS A D2
AGONIST AND WHICH IS PROVIDED FOR TREATING PARKINSONISM,
AND A METHOD FOR THE PRODUCTION THEREOF

The invention relates to a transdermal therapeutic system for the treatment of Parkinson's syndrome, comprising a backing layer which is inert to the ingredients of the matrix, a self-adhesive matrix layer containing (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol having the below-indicated formula



in an effective amount, and a protective layer which is to be removed prior to use.

World-wide about 2.5 - 3% of the population suffer from so-called Parkinson's syndrome, which breaks out mainly at the age between 58 and 62. The symptoms of this disease manifest themselves in motorial disorders such as trembling, muscle stiffening, vegetative disorders such as increased flow of saliva and tears, disturbed thermoregulation, hypopiesia and functional disorders of bladder and intestine, as well as psychic disorders such as irresolute-ness and depressive mood.

Parkinson's syndrome is caused by the degeneration of dopaminergic neurons in the substantia nigra. This leads to the depletion of dopamine in certain cerebral regions, in particular in the brain stem ganglia. The resultant disturbed balance between the neurotransmitters acetylcholine and dopamine is in the end responsible for the symptoms of the disease. A predominance of acetylcholine is responsible for the so-called plus symptoms, and a deficiency of dopamine is responsible for the so-called minus symptoms.

Parkinson's syndrome can therefore be treated with so-called anticholinergics or levodopa. Anticholinergics impede the cholinergic neurotransmission, and levodopa passes, as precursor of dopamine, the blood-brain barrier and is converted in the brain to dopamine.

Another path of treatment of Parkinson's syndrome is the treatment with dopamine receptor agonists. Dopamine agonists are substances which, although structurally different from dopamine, bind to the same receptors and trigger an effect similar to that of dopamine. Due to their molecular structure dopamine receptor agonists have properties which enable them to overcome the blood-brain barrier. In this connection it is advantageous if the substances bind selectively to a subgroup of the dopamine receptors, the D2-receptors, as this decreases side effects. In this connection, the substance (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol having the above-indicated formula, has proved an especially effective selective D2-agonist.

Due to this compound's half-life and high first-pass effect, oral administration of this substance is, however, very problematic. The short half-life would necessitate frequent intake of the substance, and the high first-pass

effect would necessitate high dosage. Whereas the intake frequency may possibly be overcome by an appropriate oral formulation, the problem of high first-pass effect can be solved in principal only by a non-oral administration of the active substance.

A transdermal system designed for the administration of a D2-agonist of the above-indicated formula has already been described in WO 94-07468. This system contains the active substance as hydrochloride in a two-phase matrix which is formed substantially by a hydrophobe polymer material, which is present as a continuous phase, with hydrated silicate dispersed therein for taking up the hydrophile drug salt, and additionally contains, or may contain, hydrophobic solvents, permeation-enhancing agents and dispersing agents.

This system has the disadvantage that the active substance salt must be mixed with the silicate in watery solution, and that an additional emulsifier is necessary to emulsify this aqueous solution with the lipophile polymer, which is dissolved in an organic solvent - commonly hexane, heptane or ethyl acetate. Due to coating problems, it is much more difficult to manufacture transdermal systems using this emulsion. In addition, for such systems only the salt can be used, since only the salt is sufficiently hydrophile to be soluble in water.

It is thus the object of the invention to develop systems for (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol avoiding the disadvantages of the system described in WO 94-07468.

In this connection, the invention particularly focuses on optimizing active substance uptake within the system, and skin transfer.

The transdermal therapeutic system according to this invention, of the kind mentioned at the beginning and developed in accordance with the above, is essentially characterized by a matrix on the basis of an acrylate-based or silicone-based non-aqueous polymer adhesive system having a solubility for the free D2-agonist base (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol of $\geq 5\%$ (w/w), which matrix is substantially free of anorganic silicate particulates. The solubility is determined at ambient temperature.

In their simplest embodiment, the matrix systems are single-phase matrices. They consist of a backing layer, an active substance-containing self-adhesive matrix, and a protective film to be removed prior to use. More complicated embodiments contain multiple-layer matrices that may also contain non-adhesive layers and control membranes.

Polyacrylates are produced by radical polymerisation of acrylic acid derivatives or methacrylic acid derivatives, it being quite possible to also use other suitable compounds such as, for example, vinyl acetate, as additional monomers. By selecting corresponding monomers it is possible to give each resultant adhesive specific properties.

It is common to crosslink polyacrylates with multivalent metal ions to enhance the physical properties of the adhesive or adapt it to the given requirements. Said metal ions are mostly used in the form of metal chelates which are soluble in organic solvents. Suitable compounds are, in particular, aluminium acetylacetonate or titanium acetylacetonate.

Silicone adhesives are in most cases polydimethylsiloxanes. However, other organic residues such as, for example, ethyl groups or phenyl groups may in principle be present instead of the methyl groups. Such silicone adhesives are available as one-component adhesives in two variants, as so-called amine-resistant and as non-amine-resistant adhesives. Due to the basic nature of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol, for a silicone adhesive containing this active substance, amine-resistant adhesives are used.

Such amine-resistant silicone adhesives stand out for their not having free silanol functions. In a special process the Si-OH groups are provided with an alkyl residue. Such adhesives and their production are described in detail in EP 0 180 377.

The adhesive's dissolving capacity for the active substance is an important parameter for the development of matrix systems, just as the mobility of the active substance in the matrix, and its transfer via the contact surface to the skin, which transfer is substantially determined by corresponding distribution coefficients and the skin absorption. This results in a relatively complicated set of influences which have to be taken into account.

In systems wherein the active substance is only partially dissolved the concentration of the dissolved active substance is equal to the saturation concentration and thus has the maximum thermodynamic activity under these conditions. In general, it is, above all, the kind and quantity of the free functional groups in the adhesive which are important for the dissolving capacity of the polyacrylate adhesives. With respect to (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol, however, it was found that the solubility of the free base is largely independent thereof, and lies in

the range of between 15 - 35% (w/w). Such a system must therefore contain the active substance in a concentration of at least 10% (w/w) in order to come sufficiently near to the maximal thermodynamic activity. For the hydrochloride of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol the solubility in polyacrylates having 5 - 10% (w/w) is much lower, so that in such systems the active substance is preferably only partially dissolved.

Since, due to its hydrophilic properties, the hydrochloride can pass the barrier of the stratum corneum only poorly, it is necessary in this case to use lipophile, monovalent acids such as, for example, oleic acid, which, in the patch matrix, partially converts the hydrochloride into the more lipophilic oleate and which, moreover, generally acts as a permeation enhancer in the skin.

Advantageously, the acrylate-based polymer adhesive contains at least two of the following monomers: acrylic acid, acrylamide, hexylacrylate, 2-ethylhexylacrylate, hydroxyethylacrylate, octylacrylate, butylacrylate, methylacrylate, glycidylacrylate, methacrylic acid, methacrylamide, hexylmethacrylate, 2-ethylhexylmethacrylate, octylmethacrylate, methylmethacrylate, glycidylmethacrylate, vinylacetate or vinylpyrrolidone.

Silicone adhesives have a comparatively low dissolving capacity for most active substances. The saturation capacity for the base (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol and the hydrochloride, respectively, is about 5% (w/w), whereas the corresponding salts are practically insoluble therein. Thus, in connection with silicone adhesives only the active substance base is suitable. If a suitable substance having an increased solubility for the active substance is admixed

to the silicone adhesive, the dissolving capacity for the free base in such matrices can be raised to up to 40% (w/w) without adversely affecting the physical properties of the matrix. Suitable substances are, for example, soluble polyvinylpyrrolidone, copolymers of vinylpyrrolidone and vinylacetate, polyethyleneglycol, polypropylene glycol, glycerol or fatty acid esters of glycerol, or copolymers of ethylene and vinylacetate, polyvinylpyrrolidone having proved particularly suitable.

About 1.5 - 5% (w/w) of polyvinylpyrrolidone in an amine-resistant silicone adhesive increase the solubility of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol to about 10 - 15% (w/w). This is sufficient to dissolve 10 mg active substance in a 20 cm² large patch having a coat weight of the matrix of 50 g/m². Since with transdermal patch systems one must always assume that only about 50% of the active substance employed will be available during the period of application, given a daily dose in the range of 1 - 10 mg of the active substance a plaster size of between 2 and 40 cm² can be expected to be sufficient to achieve therapeutic plasma levels.

The polyvinylpyrrolidone dispersed in the silicone adhesive additionally has the advantage that it decreases the so-called cold flow known from silicone adhesives. The term cold flow in this connection means that the matrix behaves like a strongly viscous fluid and thus, through flowing, tends to take up a larger area. This results in the matrix after a certain time taking up a surface which is larger than the backing layer of the patch, and in the patch tending to become agglutinated to the primary packaging material. This advantage of polyvinylpyrrolidone has already been mentioned in EP 0 524 776.

To produce the patches according to this invention,

10047200 1 2000

(-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol or the hydrochloride is dissolved or suspended in ethanol or in another suitable organic solvent, and is then added to the adhesive solution while stirring. Where the adhesive has a suitable solvent system, the active substance can also be added to the adhesive solution directly. Additional auxiliary substances can be added either to the adhesive solution, the active substance solution or to the active substance-containing adhesive solution. An auxiliary substance which advantageously is added to the active substance solution directly is, for example, an alkaline substance which is suitable of converting the active substance hydrochloride into the free active substance base. More particularly, it is preferred to use alkali metal hydroxide such as sodium or potassium hydroxide, or an alkali metal silicate such as sodium or potassium trisilicate or sodium or potassium metasilicate as the alkaline substance. After the reaction, the solution may optionally be filtered, whereby the reactants, with the exception of the active substance base, are quantitatively practically eliminated. Said reactants are sodium chloride or potassium chloride in the case that sodium hydroxide or potassium hydroxide, respectively, are used, and sodium chloride or potassium chloride and polymeric silicon dioxide in the case that sodium or potassium silicates, respectively, are used. The resultant active substance-containing adhesive solution is coated onto a suitable sheet, and the solvents are removed in a drying process. Thereafter, the backing layer of the patch is laminated onto the substantially solvent-free matrix layer, and the patches are punched out of the total laminate.

The permeation properties are advantageously enhanced by permeation enhancers which may be selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty

acid amides, glycerol or its fatty acid esters, N-methylpyrrolidone, terpenes such as limonene, α -pinene, α -terpineol, carvone, carveol, limonene oxide, pinene oxide, 1,8-eucalyptol.

Details of the production and the permeation rates achieved by the finished patches will be given in the examples and the permeation studies. The polyacrylate adhesives mentioned in Examples 1 - 3 are to be understood as examples and may be readily replaced by other acrylate adhesives suitable for medicinal use.

The finished plasters were used in permeation studies utilizing Franz diffusion cells and human epidermis. The results are listed in Figures 1 - 3. It will be seen that all plasters are capable of systemically providing a sufficient amount of active substance through the skin. The present invention demonstrates that in the case of the free bases the active substance release is markedly improved as compared to the use of salts. It will also be seen that the silicone adhesive-based plasters, although having a considerably lower active substance content, deliver approximately the same quantity of active substance via the skin as the systems based on polyacrylate adhesives.

Thus, the systems according to the invention make it possible to administer the necessary daily dose of the dopamine agonist of the structure as indicated above transdermally through the skin by means of a patch having a size of approximately 20 cm². Since the patches can be easily manufactured, and since they deliver the active substance to the skin on their entire matrix surface, and are suitable both for the active substance salts and for the active substance bases, they constitute a considerable

improvement over the known systems as described in WO 94/07468.

EXAMPLE 1: Polyacrylate system with (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol

66 g of a 50% solution of Eudragit E100 in ethyl acetate are added to 264 g of a solution of a polyacrylate adhesive having a solids content of 50%; after addition of 36 g oleyl alcohol, the mass is homogenized by stirring.

Thereafter, 89.65 g (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol are dissolved in 200 ml methylethylketone and added to the above-mentioned mass while stirring. After homogenization of the mass, it is coated onto a siliconized polyester film using a suitable doctor knife. The thickness of the moist film is adjusted such that after removal of the solvent by drying for 30 minutes at 50°C a coat weight of 60 g/m² results.

The dried matrix film is then laminated with a 13 µm-thick polyester film. From the resultant patch laminate, the finished patches are punched out at the desired size, and packed in packaging material bags.

The concentration of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol base in the patch matrix is 30.8%.

Suitable polyacrylate adhesives are, for example, Durotak 387-2051, Durotak 387-2287, Durotak 387-2353, Durotal 387-2516, all of National Starch & Chemical.

The permeation rates through human epidermis under in-vitro conditions are shown in Fig. 1.

EXAMPLE 2: Silicone system with (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol

18 g (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol dissolved in 40 g ethanol are added to 24 g of a 25% solution of Kollidon 90F and the mass is homogenized. Subsequently, 251 g of a solution of an amine-resistant silicone adhesive having a solids content of 70% are added to this mass, and the mass is homogenized by further stirring.

Subsequently, the mass is coated, using a suitable doctor knife, onto a polyester film (Scotchpak 1022) that has been rendered adhesive, at such a thickness that after removal of the solvents by drying for 30 minutes at 50°C a coat weight of 50 g/m² results.

The dried matrix film is then laminated with a 13-μm-thick polyester film. From the resultant patch laminate the finished patches are then punched out in the desired size, and packed in packaging material bags.

The concentration of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol base in the patch matrix is 9%.

Suitable amine-resistant silicone adhesives are, for example, BIO-PSA Q7-4301 and BIO-PSA Q7-4201, both by Dow Corning.

The permeation rates through human epidermis achieved under in-vitro conditions are shown in Fig. 1.

EXAMPLE 3: Polyacrylate system with the hydrochloride of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol

10 g of the hydrochloride are worked into 70 g polyacrylate adhesive (Durotak 387-2287, solids content 50%, National Starch & Chemical), and subsequently 4 g oleic acid are added. The mass is then coated onto a siliconized polyester film at such a thickness that after the removal of the solvents a coat weight of 60 g/m² results. The solvents are removed by drying for 15 - 20 minutes at a temperature between 40 and 80°C. Thereafter, the dried matrix layer is laminated with a 12 - 30 µm thick polyester film, and the patches are punched out.

EXAMPLE 4:

20 g (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol hydrochloride are stirred, together with 8.0 g sodium metasilicate or 9.1 g sodium trisilicate, in 35 ml ethanol for 48 hours, at room temperature. Optionally, the active substance solution is now filtered and 6.0 g polyvinylpyrrolidone (Kollidon F90, Bayer), in the form of a 25% (w/w) solution in ethanol, and 25 g of a 70% solution of an amine-resistant silicone adhesive (Q7-4301, Dow Corning) in heptane are added and the mass is subsequently homogenised by mechanical stirring.

For manufacture of the patch matrix, the mass is subsequently coated onto a suitable film which has been rendered adhesive, and the solvents are removed by drying for 20 minutes at 50 °C. The coat weight of the dried matrix film is approximately 50 g/m².

The dried matrix film is laminated with a 23-µm-thick polyester film. The individual patches are punched out of the complete laminate. If the active substance solution is filtered, the composition of the finished patch corresponds to that of the patch according to Example 2.

EXAMPLE 5:

25 g (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol hydrochloride are stirred, together with 14.7 g sodium metasilicate or 16.8 g sodium trisilicate, in 40 ml ethanol for 48 hours at room temperature. Optionally, the active substance solution is now filtered and 9.2 g oleyl alcohol, 63.2 g of a 52% solution of a polyacrylate adhesive (Durotak 387-2287, National Starch & Chemical) and 22.8 g of a 40% (w/w) solution of Eudragit E100 (Röhm-Pharma) are added, and the mass is subsequently homogenised by mechanical stirring.

For manufacture of the patch matrix, the mass is subsequently coated onto a suitable film which has been rendered adhesive, and the solution is removed by drying for 20 minutes at 50 °C. The coat weight of the dried matrix film is approximately 80 g/m².

The dried matrix film is laminated with a 23-µm-thick polyester film. The individual patches are punched out of the complete laminate.

EXAMPLE 6:

20 g (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol hydrochloride are added to an ethanolic NaOH or KOH solution which contains equimolar quantities of base (2.27 g NaOH, respectively 3.19 g KOH). Preferably, the solution has a concentration of 1.5 mol/l. The conversion of the active substance salt takes place within minutes, whereby the greatest part of the NaCl formed precipitates and the active substance base dissolves completely.

Optionally, a puffer solution is now added to the active substance solution in order to remove possible excess base. Likewise optionally, the active substance solution can now be filtered; 6.0 g polyvinylpyrrolidone (Kollidon F90,

Bayer) in the form of a 25% solution (w/w) in ethanol and 250 g of a 70% solution of an amine-resistant silicone adhesive (Q7-4301, Dow Corning) in heptane are added, and the mass is subsequently homogenised by mechanical stirring.

For manufacture of the patch matrix, the mass is then coated onto a suitable film which has been rendered abhesive, and the solvents are removed by drying for 20 minutes at 50 °C. The coat weight of the dried matrix film is approximately 50 g/m².

The dried matrix film is laminated with 23- μ m-thick polyester film. The individual patches are punched out of the complete laminate. If the active substance solution is filtered, the composition of the finished patch corresponds to that of the patch according to Example 2.

EXAMPLE 7:

Analogously to Example 6, 25 g (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol hydrochloride are reacted with 2.84 g NaOH, respectively 3.99 g KOH, in ethanolic solution. As in Example 6, optionally a puffer is added to the active substance solution, respectively the solution is filtered, and subsequently 9.2 g oleyl alcohol, 63.2 g of a 52% solution of a polyacrylate adhesive (Durotak 387-2287, National Starch & Chemical) and 22.8 g of a 40% (w/w) solution of Eudragit E100 (Röhm-Pharma) are added, and the mass is then homogenised by mechanical stirring.

For manufacturing the patch matrix, the mass is subsequently coated onto a suitable film which has been rendered abhesive, and the solvents are removed by drying for 20 minutes at 50 °C. The coat weight of the dried matrix film is approximately 80 g/m².

The dried matrix film is laminated with a 23- μ m-thick polyester film; the individual plasters are punched out of the complete laminate.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

CLAIMS

1. Transdermal therapeutic system, comprising a backing layer inert to the components of the matrix, a self-adhesive matrix layer containing (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol in an effective amount and a protective foil or sheet to be removed prior to use, characterised by a matrix that is based on a non-aqueous, acrylate-based or silicone-based polymer adhesive system having a solubility of $\geq 5\%$ (w/w) for (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol, and said matrix is substantially free of inorganic silicate particulates.
2. Transdermal therapeutic system according to claim 1 that contains $< 0.5\%$ (w/w) inorganic silicate particulates.
3. Transdermal therapeutic system according to claim 1 that contains $< 0.05\%$ (w/w) inorganic silicate particulates.
4. Transdermal system according to claim 1 in which the acrylate-based polymer adhesive contains at least two of the following monomers: acrylic acid, acrylamide, hexylacrylate, 2-ethylhexylacrylate, hydroxyethylacrylate, octylacrylate, butylacrylate, methylacrylate, glycidylacrylate, methacrylic acid, methacrylamide, hexylmethacrylate, 2-ethylhexylmethacrylate, octylmethacrylate, methylmethacrylate, glycidylmethacrylate, vinylacetate or vinylpyrrolidone.
5. Transdermal system according to claim 1 in which the silicone-based polymer adhesive includes additives to enhance the solubility of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol in the form of hydrophilic polymers or glycerol or glycerol derivatives.

6. Transdermal system according to claim 4 or 5 in which (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol is contained in the acrylate-based polymer adhesive in a concentration of from 10 to 40% (w/w), or in the silicone-based polymer adhesive in a concentration of from 5 to 25% (w/w).
7. Transdermal system according to claim 6 that contains substances that enhance the permeation of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol into the human skin.
8. Transdermal system according to claim 7 in which the permeation-enhancing substance is selected from the group of fatty alcohols, fatty acids, fatty acid esters, fatty acid amides, glycerol or its derivatives, N-methyl-pyrrolidone, terpenes or terpene derivatives.
9. Transdermal system according to claim 8 in which the permeation-enhancing substance is oleic acid or oleyl alcohol.
10. Transdermal system according to claim 5, in which the hydrophilic polymer is polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinylacetate, polyethyleneglycol, polypropylene glycol or a copolymer of ethylene and vinylacetate.
11. Transdermal system according to claim 10 wherein the hydrophilic polymer is soluble polyvinylpyrrolidone being present in the active substance-containing matrix layer at a concentration of 1.5 - 5% (w/w).
12. Transdermal system according to claim 1 in which the matrix contains inert fillers to improve cohesion.

13. A process for preparing a transdermal therapeutic system, comprising the following steps:

- i) mixing a suspension of (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol hydrochloride in ethanol with an alkaline compound in ethanol to convert the hydrochloride into the free base,
- ii) optionally filtering the resultant suspension,
- iii) adding polyvinylpyrrolidone and a solution of an adhesive, and iv) drying the product.

14. A process according to claim 13 wherein, as alkaline compound, sodium hydroxide or potassium hydroxide are used.

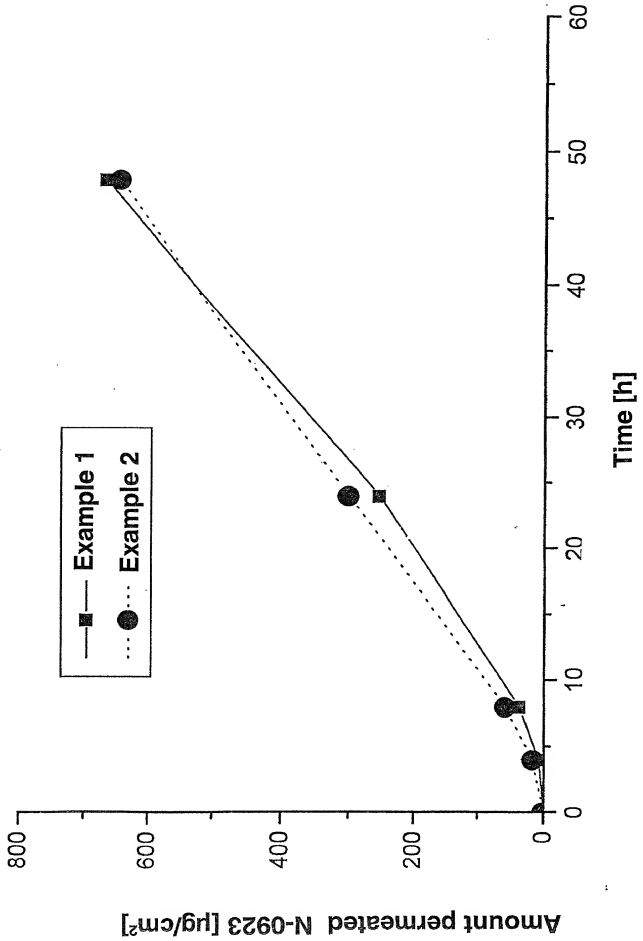
15. A process according to claim 13 wherein, as alkaline compound, sodium metasilicate or potassium metasilicate, or sodium or potassium trisilicate are used.

16. The process of claim 13 wherein before drying the product, the mixture is spread on an inert backing layer or protective foil or sheet in such a manner as to produce a uniform film.

17. A product prepared by a process according to one of the claims 13 to 16.

ABSTRACT

A transdermal therapeutic system, comprising a backing layer inert to the components of the matrix, a self-adhesive matrix layer containing (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthalenol in an effective amount and a protective foil or sheet to be removed prior to use, is characterised by a matrix that is based on a non-aqueous, acrylate-based or silicone-based polymer adhesive system having a solubility of $\geq 5\%$ (w/w) for (-)-5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]-amino]-1-naphthalenol, and said matrix is substantially free of inorganic silicate particulates.



Attorney Docket No.: **FLA-0048****COMBINED DECLARATION AND POWER OF ATTORNEY**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and

I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **Transdermal Therapeutic System Which Contains a D2 Agonist and Which is Provided for Treating Parkinsonism, and a Method for the Production Thereof** the specification of which:

() is attached hereto.

(XX) was filed on 18 March, 1999 as Application Serial No. PCT/EP99/01795 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to the patentability of this application in accordance with 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of any application on which priority is claimed:

Country	Number	Date Filed	Priority Claimed			
German	198 14 084.3	30 Mar. 1998	Yes	X	No	
			Yes		No	
			Yes		No	

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: **Jane Massey Licata**, Registration No. 32,257, **Kathleen A. Tyrrell**, Registration No. 38,350, and **Laura M. Plunkett**, Registration No. 45,015 of the firm of **Law Offices of Jane Massey Licata**, 66 East Main Street, Marlton, New Jersey 08053, and

Address all telephone calls and correspondence to:

Jane Massey Licata, Esq.
Law Offices of Jane Massey Licata
66 East Main Street
Marlton, New Jersey 08053

Telephone No.: (856) 810-1515

I hereby declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1	Full Name: <u>Walter Müller</u>	Inventor's Signature: <i>Walter Müller</i>	Date: <u>04.10.00</u>
	Residence: Engerser Strasse 56 Neuwied, Germany D-56564 <i>DE</i>	Citizenship: German	
	Post Office Address: Same as above.		
2	Full Name: <u>James V. Peck</u>	Inventor's Signature: <i>James V. Peck</i>	Date: <u>11/20/00</u>
	Residence: 10821 Millington Lane Richmond, Virginia 23233 <i>VA</i>	Citizenship: US	
	Post Office Address: Same as above.		
3	Full Name:	Inventor's Signature:	Date:
	Residence:	Citizenship:	
	Post Office Address: Same as above.		
4	Full Name:	Inventor's Signature:	Date:
	Residence:	Citizenship:	
	Post Office Address: Same as above.		